

## **II. RESPONSE TO OFFICE ACTION**

### **A. State of the Claims**

Claims 1-11 were pending prior to the Office Action dated June 17, 2003. Claim 1 has been amended in the Amendment submitted herewith. Claims 2-3 and 12-62 have been canceled without prejudice or disclaimer. New claims 63-70 have been added. Therefore, claims 1, 4-11, and 63-70 are presently pending.

Each of these new claims is fully supported by the specification. For example, page 58, lines 9-14, provide information pertaining to the limitation “wherein the DNA encodes an amino acid sequence that is at least 70% identical to SEQ ID NO:2.” Page 20, line 12 through page 21, line 5 provide information pertaining to the limitation “wherein the DNA comprises 500 contiguous nucleotides that are identical or complementary to SEQ ID NO:1.

Applicants assert that the amendment should be entered because it addresses issues set forth by the Examiner in the previous Office Action (*i.e.*, the inclusion of structural limitations to the claims, further addressed in the responses below). In addition, the amendment does not necessitate a new search. For all of these reasons, entry of the amendment is respectfully requested.

### **B. Drawings**

The Action notes that in order to avoid abandonment, the drawing informalities noted on PTO-948 attached to Paper No. 8, mailed on September 6, 2002, must now be corrected. Applicants have submitted the corrected drawings.

### C. Claims 1-4 and 6-11 Are Definite

The Action maintains a rejection of claims 1-4 and 6-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. It contends that the specification defines “infectious nucleic acid” as full-length cDNAs or RNA transcripts that are infectious in cell culture. The Action further argues that the term “isolated and purified” is defined as a nucleic acid molecule that is not part of an intact GBV-C virus. It concludes that the claim is not clear because it can be interpreted in two ways: (1) to require full-length cDNA and RNA transcript that is different than those described because it is able to replicate *in vitro*; or (2) to involve less than a full-length clone, requiring anywhere from 10-12000 nucleotides. Applicants traverse this rejection.

The Action is incorrect about the specification’s definition of “infectious nucleic acid.” In support of the definition, the Action cites page 6, lines 8-20 and page 18-19 of the specification.

On page 6, the specification, the subheading “Infectious Nucleic Acids” is under the general heading of “Description of Related Art” and the text accompanying the subheading describes the art and its teaching of infectious nucleic acids—the text does not describe the present invention. The text states: “Full length cDNA or RNA transcripts of several RNA viruses including hepatitis A virus, GBV-B, and HCV are infectious in cell culture or animal inoculation studies. . . .” (citations omitted). Notably, GBV-C is absent from that description. It is inappropriate to use a characterization of what the prior art has taught to define the present invention. Furthermore, simply because the subheading is “Infectious Nucleic Acids” does not mean that a description of what the prior art has taught is a complete definition of that

subheading, as opposed to examples of what qualifies as an infectious nucleic acid. Thus, this section of the specification, which describes related art, does not describe the present invention.

On page 19, lines 1-2, the specification states that “[a]n infectious GBV-C nucleic acid molecule refers to an RNA or DNA molecule that is capable of yielding an infectious GBV-C particle from a transfected cell.” Applicants draw the Examiner’s attention to the fact that this definition does not require that the DNA or the RNA molecule be a full-length DNA or RNA molecule. On page 19, lines 3-13, the specification distinguishes between “RNA transcript” and “full-length RNA transcript.” An RNA transcript refers to “an RNA molecule that has been isolated free of total genomic viral RNA and virus proteins and that is the product of transcription from a nucleic acid molecule for which at least one strand is DNA.” Specification, page 19, lines 3-5. This is to be distinguished from a “full-length RNA transcript,” which refers to “an RNA transcript that is full-length when compared to the genomic coding region, for example of GBV-C.” Specification, page 19, lines 5-7. One of ordinary skill in the art would understand, from reading these sections of the specification, that “infectious nucleic acid” includes not only full-length nucleic acid molecules, but also nucleic acid molecules that are not full-length.

There is no reason that a person of ordinary skill in the art would believe that infectious nucleic acids are *limited* to full-length cDNAs or RNA transcripts; instead, that person reading the specification would understand that some examples of infectious nucleic acids of viruses other than GBV-C virus have been full-length.

The specification provides other information that makes clear that the term “infectious nucleic acids” is not limited to full-length sequences. Under the section “Summary of the Invention,” the specification states:

The compositions and methods of the present invention take advantage of the discovery of an isolated and purified nucleic acid molecule encoding an infectious GBV-C. . . . These nucleic acid molecules have been produced in the form of a DNA construct or expression construct, as well as an infectious full-length GBV-C RNA transcript expressed from the DNA construct (collectively referred to as "recombinant GBV-C"). A cDNA clone made from the full-length or a less-than full-length transcript is also contemplated within the scope of the invention.

Specification at pp. 6-7. Thus, full-length and less-than full-length transcripts are understood as part of the invention.

The claims are directed to an "isolated and purified DNA encoding an infectious GBV-C." The standard for definiteness of a claim is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with "a reasonable degree of certainty." *MPEP* 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)). The specification indicates that the phrase "isolated and purified" refers to a "nucleic acid molecule [that] is not part of an intact GBV-C virus." Specification at page 6. Furthermore, the specification also makes it clear that a nucleic acid molecule encoding an infectious GBV-C refers to a nucleic acid that is infectious and contains GBV-C sequence. Specification at page 7.

The examiner pursues a discussion of functional versus structural claim language, noting that the term "infectious" refers to a function rather than to a specific structure. However, this discussion is irrelevant in determining whether a claim meets the standard for definiteness.

As noted by the Examiner, "[a] patent applicant is free to recite features of an apparatus either structurally or functionally." Office Action, page 4, citing *In re Swinehart*, 439 F.2d 210, 212, 169 USPQ 226, 228 (CCPA 1 971) ("[T]here is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims.") Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. *MPEP* §2173.01. As noted by the court in *In re Swinehart*, a claim may not be rejected

solely because of the type of language used to define the subject matter for which patent protection is sought. MPEP, § 2173.01 citing *In re Swinehart*, 439 F.2d 210. Thus, use of functional claim language is not grounds for a rejection for lack of definiteness.

As noted above, the standard for definiteness of a claim is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with a reasonable degree of certainty. The Examiner's discussion pertaining to the use of functional claim language fails to raise any doubt that the scope of the claims can be determined by one of ordinary skill in the art with reasonable certainty. Indeed, the Examiner has failed to set forth any basis whatsoever for contending that a person of ordinary skill in the art would be unable to determine the scope of claim 1 with reasonable certainty. Consequently, Applicants respectfully request that this rejection be withdrawn.

#### **D. Claims 1-4 and 6-11 Are Enabled**

The Action maintains a rejection of claims 1-4 and 6-11 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for an infectious nucleic acid that is less than or greater than the full-length clone. While the Action admits the specification is enabled for an infectious full-length clone of GBV-C that corresponds to SEQ ID NO:1, it argues that a single example utilizing a full-length clone does not provide sufficient guidance to make infectious clones that may be smaller or larger in size.

The Action cites Pang *et al.* ("Pang") as supporting its position that the art is unpredictable because this article purportedly shows that structural proteins can be replaced with heterologous sequences, but that the resulting nucleic acids are not infectious and do not produce particles. It concludes that one of ordinary skill in the art would not be able to reproducibly

practice the entire scope of the invention as claimed, without undue experimentation. Applicants traverse this rejection.

In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has “acceptable evidence or reasoning” to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971). The PTO thus must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982).

As noted by the Action, it has been held that a prior art reference must either be in the field of Applicants’ endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

Applicants assert that the Pang reference is not in the Applicants’ field of endeavor and that it is not reasonably pertinent to the particular problem addressed by the Applicants. In support of its assertion that Pang is pertinent, the Examiner notes that the Pang reference pertains to a flavivirus, and that GBV-C is also a flavivirus. The Action also cites the Pang reference because it purportedly shows an attempt to produce infectious virus from a replicon RNA that contained heterologous sequences in place of endogenous viral genes. However, this reference does not shift the burden to the applicant because the Pang reference has nothing to do with hepatitis viruses, much less GBV-C. The Pang reference is entitled “Development of

dengue virus replicons expressing HIV-1 gp120 and other heterologous genes: potential future tool for dual vaccination against dengue virus and HIV.”

The Pang reference describes engineered nucleic acid molecules from the dengue virus, which is not a hepatitis virus. Furthermore, the Pang reference makes it clear that the authors are attempting to engineer a vaccine against dengue virus, in which case they *do not want* an infectious nucleic acid. This is supported by their Conclusion in which they state: “Although our successful development of a plasmid which can express a dengue replicon from transfected DNA facilitates delivery by DNA vaccination, the development of packaging cell lines which can package these replicons into virions would be a major step forward towards a vaccine . . . .” Pang at p. 6. Because the Pang reference indicates the authors were trying to avoid obtaining an infectious nucleic acid, precisely what the claimed invention concerns, and that they successfully were able to achieve such a noninfectious nucleic acid says nothing about the claimed invention. This says nothing about the claimed invention. It has no relevance regarding the unpredictability in the art about what size of heterologous sequence can be inserted into the GBV clone while maintaining infectiousness.

Applicants respectfully note that “it is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” MPEP 2164.04 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). The Action’s only reasoning is that the Pang reference utilized a flavivirus construct. However, this reason alone is not acceptable, particular when the reference not only failed to accomplish a particular goal of the present invention - *i.e.*, production

of infectious nucleic acids with substitutions, but also makes it clear that it wanted to avoid such a goal. Thus, the evidence put forth by the Action to back up its assertion is insufficient.

Moreover, the test of enablement is whether the experimentation needed to practice the invention is undue. *MPEP* § 2164.01 (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). There is no reason a person of ordinary skill in the art could not use the teachings of the specification to generate additional infectious GBV-C nucleic acids.

Although Applicants assert that the claims as originally written were enabled, Applicants draw the Examiner's attention to the amendment to claim 1. The amendment to claim 1 adds the limitation that the nucleic acid molecule is a DNA molecule, and adds the limitation "wherein the DNA encodes an amino acid sequence that is at least 70% identical to SEQ ID NO:2. New claims 63-70 have been added, which depend from claim 1. Claim 65 includes the limitation "wherein the DNA comprises 500 contiguous nucleotides that are identical or complementary to SEQ ID NO:1. Claim 69 includes the limitation "wherein the DNA comprises a 3' ntr or a 5' ntr of GBV-C.

Applicants assert that in view of the amendment to claim 1, the specification provides structural requirements necessary to make a GBV-C nucleotide sequences of the claimed invention. In particular, the specification provides the full-length DNA sequence of an isolated and purified DNA sequence of an infectious clone (*i.e.*, SEQ ID NO:1). In addition, the specification provides the protein sequence encoded by this nucleic acid sequence as SEQ ID NO:2.

The instant specification shows how to construct an infectious GBV-C nucleic acid (Examples 1 and 2), as well as how to analyze it and assay it for infectivity (Examples 3 and 4). The generation of deletions, substitutions, insertions and other additions is well known to those

of ordinary skill in the art through the use of recombinant nucleic acid technology. On pages 18-36, basic information regarding the manipulation of nucleic acids is provided. The instant specification also provides information pertaining to the 3' ntr and 5' ntr of GBV-C (Example 3).

Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). In view of the fact that the specification clearly discloses, in SEQ ID NO:1, an example of an infectious clone, one of ordinary skill in the art would be able to use this information as a starting point to generate other infectious clones. The level of ordinary skill of one in the art is high, and although some experimentation may be involved, it is certainly not undue experimentation.

Accordingly, Applicants respectfully request this rejection be withdrawn.

**E. The Claims Are Not Anticipated by the Prior Art**

**1. Claims 1-4, 6-7, and 9-10 Are Not Anticipated by Kim *et al.***

The Action maintains its rejection of claims 1-4, 6-7, and 9-10 under 35 U.S.C. § 102(b) as being anticipated by Kim *et al.* (U.S. Patent No 5,856,134) ("Kim"). It contends that Kim discloses the entire coding region of two hepatitis-G virus DNA clones and that it further discloses the "expression and purification of HGV virus protein [sic]." (Applicants have assumed the Action meant an HGV virus "particle.") The Action interpreted the claims of the instant invention to encompass sequences that are less than full-length GBV-C, and consequently, determined the claims were anticipated by Kim.

The examiner also cites *In re Schreiber* for the proposition that when the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in

the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the Applicants to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. *In re Schreiber*, 128 F.3d 1473, 1431, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). The Action asserts the rejection should be maintained because it has reason to believe that infectivity is an inherent characteristic of the Kim reference, and because the Applicants have not pointed to structural differences that are required to distinguish the claimed invention over the cited prior art. Applicants respectfully traverse this rejection.

Applicants draw the Examiner's attention to amended claim 1, which recites "an isolated and purified DNA encoding an infectious GBV-C, wherein the DNA encodes an amino acid sequence that is at least 70% identical to SEQ ID NO:2." As noted above, the rejection pertaining to claims 2 and 3 is moot since these claims have been canceled. The remaining claims that are the subject of this rejection depend from amended claim 1.

Applicants assert that there is no reasonable basis for the Action to conclude that infectivity is an inherent characteristic of the clones disclosed in the Kim reference. In particular, prior to the present application, no one had shown such a molecule existed. Applicants draw the Examiner's attention to page 16, lines 24-26 of the instant Specification, which indicates that "[w]hile sequences of GBV-C have been previously reported, for example in U.S. Patent No. 5,874,563, which is specifically incorporated by reference, an infectious GBV-C clone has not been previously reported." Thus, based on the state of the art at the time of filing of this application, there was **no reasonable basis** to conclude that the Kim reference would teach clones that were infectious.

Because there is no reasonable basis to draw this conclusion, Applicants should not have to prove, in accordance with *In re Schreiber*, that the clones disclosed in the Kim reference are

not infectious. Indeed, Applicants were the first to invent an infectious nucleic acid that was isolated away from GBV-C viral particles. The Kim reference does not teach any such nucleic acid molecule, nor does the Action identify any disclosure of such a molecule in the Kim reference.

Even though Applicants are not required to provide evidence of infectivity under the standard of *In re Schreiber*, Applicants herein provide evidence of noninfectivity of the Kim reference clones. In support of the assertion that the clones disclosed in Kim are not infectious, Applicants herein submit the second declaration of Jack Stapleton, M.D (hereinafter the “Second Stapleton Declaration”).

Genelabs, Inc., the owner of the U.S. Patent known as the Kim reference, provided Dr. Stapleton with a clone to test for infectivity and a serum sample from which the clone was obtained. See, generally, the Second Stapleton Declaration, paragraphs 5 and 6. The clone, which linked small fragments disclosed in the Kim reference, was not constructed before 2002, and neither the clone nor the serum from which the clone was prepared was ever tested for infectivity.

Dr. Stapleton’s laboratory performed assays on the Kim reference clone and the serum sample to test for infectivity which were similar to those described in Examples 4 and 5 of the present patent application. See, generally, Second Stapleton Declaration, paragraph 7. None of the samples obtained 2 or more weeks post-transfection demonstrated production of GBV-C RNA and GBV-C virus particles could not be recovered from transfected cells. Second Declaration, paragraph 7. In addition, the serum sample did not yield persistent infection. Thus, neither the Kim reference clone nor the serum sample from which it was obtained were found to

be infectious. See, generally, the Second Stapleton Declaration, paragraphs 8-11. Furthermore, Dr. Stapleton is unaware that Genelabs possesses any other putative infectious clones.

In view of the above, Applicants assert that the sequences disclosed in the Kim reference, including SEQ ID Nos: 14 and 182, do not possess the required element of being an infectious GBV-C DNA. The Second Stapleton Declaration provides ample evidence that the Kim reference does not teach an “isolated and purified DNA encoding an infectious GBV-C.”

Without a disclosure of an *infectious* GBV-C virus or clone, the Kim reference *does not teach an element of the claimed invention*. Accordingly, the Kim reference does not anticipate the claimed invention.

For all of the above reasons set forth above, the Kim reference does not anticipate claims 1-4, 6-7, and 9-10. Applicants respectfully request this rejection be withdrawn.

## **2. Claims 1 and 2 Are Not Anticipated by Xiang *et al.***

The Action rejects claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Xiang *et al.* (“Xiang”). As noted above, claim 1 has been amended in the amendment contained herein, and the rejection of claim 2 is moot since claim 2 has been canceled.

Xiang is said to disclose RNA extraction (isolation and purification) of HGV RNA from patient plasma samples. The Action concludes that Xiang anticipates the claimed invention to the extent the claims are interpreted to as sequences that can be less than full-length GBV-C. Applicants respectfully traverse this rejection.

Again, in order for a reference to anticipate a claim, each element of the claim must be disclosed or taught in the cited reference. The Xiang reference does not teach an “infectious” nucleic acid molecule. It does not mention any assays being conducted to determine whether the

isolated molecules were infectious. In fact, according to the Declaration, the infectivity of isolated GBV-C RNA molecules was never tested.

In addition, the Declaration notes that Xiang pertains to the isolation of HGV RNA molecules. Declaration, paragraph 7. Amended claim 1 recites “isolated and purified DNA encoding an infectious GBV-C, wherein the DNA encodes an amino acid sequence that is at least 70% identical to SEQ ID NO:2.” Xiang does not teach isolated and purified DNA, and thus it also fails to teach DNA encoding an amino acid sequence that is at least 70% identical. Thus, Xiang fails to teach the structural limitation of the claimed invention.

Accordingly, Xiang fails to teach any element of the claimed invention. Therefore, it does not anticipate claim 1. Applicants respectfully request this rejection be withdrawn.

### **3. Claims 1-3, 6, and 9-11 Are Not Anticipated by Pilot-Matias *et al.***

The Action rejects claims 1-3, 6, and 9-11 under 35 U.S.C. § 102(e) as being anticipated by Pilot-Matias *et al.* (U.S. Patent No. 6,156,495) (“Pilot-Matias”). It contends that Pilot-Matias discloses the production of fusion proteins comprising HGBV virus sequences, the nucleic acids encoding the HGBV virus sequences are inserted into a pSFV1 construct, which contains the heterologous promoter Sp6. As such, the Action contends that the instant claims are anticipated by Pilot-Matias *et al.* Applicants respectfully traverse this rejection.

As disclosed in the specification of the present application, what was invented by the inventors was a GBV-C nucleic acid that is infectious and not included in a viral particle. The cited references, including the Pilot-Matias reference, fail to anticipate the claimed invention because the inventors of the present application were the first to disclose an isolated and infectious GBV-C nucleic acid. The Declaration states that the Pilot-Matias reference “does not

show the infectivity of any nucleic acids from a GBV-C, nor does it show that the serum from which GBV-C particles was isolated contains infectious virus.” Declaration, paragraph 8.

Moreover, Pilot-Matias discloses recombinant polypeptides (column 3, line 56), and not isolated and purified DNA encoding an infectious GBV-C, wherein the DNA encodes an amino sequence that is at least 70% identical to SEQ ID NO:2. Because GBV-C is an RNA virus, any nucleic acid from a viral clone would be composed of RNA and not DNA. There is no indication that any DNA molecules were generated, much less infectious ones. Thus, Pilot-Matias fails to disclose every element of the claimed invention.

Patent law requires identity between the reference and the claimed invention. Having fallen short, the Pilot-Matias reference cannot anticipate the claimed invention. Applicants respectfully request this rejection be withdrawn.

#### **F. Conclusion**

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner’s supervisor, and the undersigned attorney at (512) 536-3081 is respectfully requested.

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Date: August 18, 2003

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